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On selecting markers for association studies: patterns of linkage disequilibrium between two and three diallelic loci.

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Association studies depend on linkage disequilibrium (LD) between a causative mutation and linked marker loci. Selecting markers that give the best chance of showing useful levels of LD with the causative mutation will increase the chances of successfully detecting an association. This report examines the variation in the extent of LD between a disease locus and one or two diallelic marker loci (termed single nucleotide polymorphisms or SNPs). We use a simulation method based on the neutral coalescent in a population of variable size to find the distribution of LD as a function of allele frequencies, the recombination rate, and the population history. Given that LD exists, the allele frequencies determine if a site will be useful for detecting an association with the disease mutation. We show that there is extensive variation in LD even for closely linked loci, implying that several markers may be needed to detect a disease locus. The distribution of LD between common variants is strongly influenced by ancestral population size. We show that in general, best results will be obtained if the frequencies of marker alleles are at least as large as the frequency of the causative mutation. Haplotypes of two or more SNPs generally have a higher probability than individual SNPs of showing useful LD with a disease mutation, although exceptions are described.

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